Selected Paper of note: see citations 35, 46, 48, 93,81, 114

PI Frank Gilliland MD PhD

SUMMARY REPORT OF PROGRESS

The Children's Environmental Health Center (CEHC) was established in 1998 to investigate effects of the environment on children's respiratory health, with a focus on asthma and airway disease. In the following sections, we provide an overview of the contributions made by the CEHC. The Center's organization and mechanisms have allowed us to ask broad scientific questions that require an integrated multidisciplinary team to answer efficiently, and at the same time, provide multidisciplinary training for the next generation of environmental health scientists. We focus on how the integrative and collaborative multidisciplinary structure and flexibility of the Center have promoted the development of effective teams of researchers who tackle timely and important scientific problems to efficiently advance environmental health research and translation of research findings into action.

Over the years since the CEHC's founding, we have made major contributions in multiple timely and important scientific and translational arenas, including three areas highlighted in the following sections:

(1) Identifying clinically significant adverse effects of ambient air pollution on children's respiratory health;
(2) Demonstrating that common genetic variants are major contributors to children's susceptibility to environmental stressors;
(3) Defining important pathophysiologic mechanisms for the chronic effects of air pollutants on children's respiratory health; and
(4) Translating research findings to elevate environmental health effects into an essential element for decision-making in urban planning and economic development in southern California.

Identifying Clinically Significant Adverse Effects of Ambient Air Pollution on Children's Respiratory Health

As described in several high-impact publications, we have observed that children exposed to elevated levels of ambient air pollutants including ozone, PM, NO_2 and fresh traffic-related emissions show clinically important adverse effects on asthma pathogenesis, lung function development, respiratory symptoms and infections.[1-13] The Center facilitated the multidisciplinary collaborations that led to the development of cutting-edge exposure assessment methodology integrating spatial statistics, home-based measurement of air pollutants, environmental multi-level statistical modeling, geographical information systems (GIS), meteorology, and epidemiology. Several important papers documenting the adverse respiratory health effects of regional pollution relied on data developed by the exposure assessment core from measurements at regional monitoring sites and statistical models developed for these analyses.[1, 9-10, 14] In order to assess the impact of local exposures due to fresh traffic emissions, new residential and school exposure indices were developed, based on traffic volume, wind speed and direction and mixing layer height, using a GIS system. Using these models, we have demonstrated associations of asthma prevalence and incidence with traffic-modeled pollution and proximity to major roadways.[3, 6] We have now collected pollution data from a dense network of locations in each of our study communities. Using these measurements and spatial statistical techniques in a Bayesian framework, we have developed new methods for examining effects of traffic-related air pollution.[15] With the development of sophisticated statistical techniques and the advancement of exposure assessment technology (neither of which would have occurred without Center support) we were able to identify independent adverse pulmonary effects from both regional and local pollution.[5] This observation will clearly have an impact on the policy approaches to dealing with this dual problem.

Demonstrating that Common Genetic Variants are Major Contributors to Children's Susceptibility to Environmental Stressors

The task of decreasing children's susceptibility to air pollution offers an important strategy that can be used to target public health prevention efforts. Emerging research indicates that modifiable antioxidant defenses may be an important response to air pollution. Airborne particulate pollutants, such as DEPs, are thought to exacerbate lung and cardiovascular diseases through induction of oxidative stress.[16] The role of genes involved in oxidative stress produced by xenobiotics (phase II enzymes) has been examined by using GST genotypes, including *GSTM1* and *GSTT1*, which have a null genotype resulting in no protein product, and *GSTP1*, which has a well-studied functional variant (Ile105Val). In individuals with *GSTM1*-null or *GSTP1*-Ile105 genotypes, DEPs enhanced nasal responses to allergen.[17] Compared to subjects with a functional *GSTM1* genotype, *GSTM1*-null subjects had significantly larger increases in IgE levels (146 vs 13.5 U/mL; $P < .01$) and histamine levels (13.9 vs 6.1 nmol/L; $P = .03$) after a DEP plus allergen challenge. The wild-type

GSTP1 genotype was associated with increased IgE levels (149 vs 29.6 U/mL; $P < .01$) and histamine levels (14.5 vs 6.1 nmol/L; $P = .01$) after the same challenge. None of the GSTs modified the response to allergen alone. Common polymorphisms in *GSTM1* and *GSTP1* powerfully modify the adjuvant effect of DEPs on allergic inflammation and identify a large population susceptible to adverse health effects of DEP exposure.

Defining Important Pathophysiologic Mechanisms for the Chronic Effects of Air Pollutants on Children's Respiratory Health

A growing body of evidence indicates that acute and chronic inflammation contributes to the pathogenesis of several common respiratory diseases and conditions.[18-21] Oxidative and nitrosative stress play important roles in regulating immune responses and subsequent tissue responses. Oxidative/nitrosative stress occurs when oxidant and/or nitrosant burden exceeds the buffering capacity of airway antioxidant/nitrosant defenses.[22] In the previous grant period, we investigated whether high ambient air pollutant exposures are associated with airway inflammation as assessed by exhaled nitric oxide (FeNO measured at the conventional 50ml/sec flow rate) in more than 2700 children. We found that exposures to $PM_{2.5}$ mass concentration (seven-day average prior to the test) were associated with increased FeNO. We then investigated whether genetic variants were associated with airway inflammation and children's susceptibility to airway inflammation from ambient air pollution. We found substantial evidence that variation in several genes in the NO synthesis pathway including *NOS2A* and *ARG2* are associated with FeNO, susceptibility to air pollution, risk of new onset asthma and lung function growth. Lastly, we determined that children with chronic airway inflammation as indicated by elevated FeNO are at a greater than two-fold increased risk for new onset asthma. The Center's studies of eNO, along with the studies of genetic variants in oxidative stress and inflammatory pathways provide strong support for the role of oxidative/nitrosative stress in mediating the effects of ambient air pollution.

One approach to reducing the effects of air pollutants such as DEPs is through induction of enzymatic antioxidant defenses, especially in individuals with at-risk genetic variants of key antioxidant enzymes. A prototype for this approach is dietary induction of phase II metabolic enzymes to protect against DEPs. In a proof-of-principle study, dietary sulforaphane, a potent inducer of phase II enzymes, was shown to increase enzyme expression and reduce inflammatory responses.[23] In an in vitro cell system, Wan and Diaz-Sanchez[23] investigated whether sulforaphane stimulated phase II enzyme induction and subsequently reduced the effect of diesel extracts on cytokine production. Sulforaphane increased *GSTM1* and *NQO1* expression, as well as GST activity, while reducing cytokine production. In primary bronchial epithelial cells, sulforaphane also blocked the increased production of interleukin 8, granulocyte-macrophage colony-stimulating factor, and interleukin 1β from primary human bronchial epithelial cells. DEPs have been shown to increase the production of IgE for *in vitro* cell systems and human nasal challenges. The induction of phase II enzymes in B cells by sulforaphane has been shown to reduce the ability of DEPs to increase IgE production.[23] Dietary sulforaphane also increases phase II enzyme expression in nasal cells. These results suggest that sulforaphane or other compounds that induce phase II enzymes have promise as air pollution chemopreventive agents.[24] These chemopreventive effects also might be available through dietary modification. Further research is needed to determine whether the adverse effects of air pollution can be reduced through interventions tailored to individual genetic susceptibility.

Translating Research Findings to Elevate Environmental Health Effects into an Essential Element for Decision-Making in Urban Planning and Economic Development in Southern California

Decisions about urban planning and regional economic development have important long-term implications for children's health, and in general, have not considered the impacts of exposure to environmental air pollution. Major decisions about the urban infrastructure in southern California and the changing global economy present an opportunity for the Center to have lasting impacts on children's health by translating Center findings about the adverse effects of air pollution to decision-makers and stakeholders. The Community Outreach and Translation Core (COTC) has succeeded in discussing environmental health as a central consideration in the debate about alternative development scenarios, creating effective programs for translation of the scientific findings, and providing community members and groups with the knowledge and tools needed to allow these stakeholders to more effectively have their concerns heard. This high-impact effort has the potential to improve health and prevent disease in millions of children for generations to come.

At the inception of our Center in 1998, the issue of air pollution from the ports and goods movement was not a high priority for regulatory agencies, scientists or even many community residents in the harbor area. The volume of cargo containers handled at the Ports of Los Angeles and Long Beach has doubled since that time. Today these adjacent ports are the largest port complex in the United States and the number one single source of air pollution in the region, in part due to lack of emission regulations on foreign-flagged ships and the

use of older diesel trucks to transport containers out of the Ports. Even with the economic slowdown, the Ports continue to anticipate a doubling of Asian imports into the Ports by the year 2030. Plans are underway to expand marine terminals, freeways, rail yards and other transportation infrastructure to accommodate the flow of goods (half of which are destined for other parts of the country). The COTC and Center investigators first became aware of the emerging situation in 2001 by listening to residents of port communities at our NIEHS Town Meeting, co-sponsored by the CEHC. Since 2001, the COTC has worked to integrate concerns about air pollution's adverse health impacts and related health costs into transportation and land-use decisions, where health concerns previously have seldom been a priority. This effort has led to the participation of center investigators Andrea Hricko and Ed Avol in dozens of regional planning, regulatory, port, and transportation committee meetings. The COTC has also educated dozens of community groups about relevant research findings. Our Center has been recognized for its expertise on the environmental health impacts of international trade, ports and goods movement, by appointment of the COTC director to US EPA's National Environmental Justice Advisory Council's "Goods Movement Work Group," and appointment of Center investigators Hricko and Avol to formal stakeholder committees of the Ports and Metropolitan Transportation Authority.

Summary of Key Research Findings from the Previous Cycle

The CEHC has yielded a wealth of data on the acute and chronic respiratory effects of air pollutants; gene-environment interactions; host susceptibility to air pollutants; novel spatial modeling approaches and methods; and exposure assessment methodology. The interdisciplinary nature of this Center has made it possible to develop an integrated program that is synergistic and provides a larger return on investment than would a single investigator model. In this section, we briefly summarize key research findings from the previous cycle.

Health Effects of Air Pollution and Tobacco Smoke Exposures

1. Current levels of air pollution have chronic, adverse effects on lung development in children from the age of 10 to 18 years, leading to clinically significant deficits in attained FEV_1 as children reach adulthood.[8]
2. Respiratory health in children is adversely affected by local exposures to outdoor NO_2 or other freeway-related pollutants.[25]
3. Residential traffic exposure is associated with deficits in lung function growth.[26]
4. Residential traffic exposure is associated with prevalent asthma, lifetime asthma and wheezy phenotype.[3, 27]
5. New onset asthma in primary school children is independently associated with local traffic-related pollution near homes and near schools.[28-29]
6. Markers of traffic-related air pollution are associated with the onset of asthma, providing further evidence that air pollution exposure contributes to new cases of asthma.[30-31]
7. On-road commuting exposure to air pollution increases the risk of asthma.[32]
8. Maternal and grandmaternal smoking during pregnancy may increase the risk of childhood asthma.[33]
9. Regular cigarette smoking increases the risk for new onset asthma among adolescents, especially among those exposed to maternal smoking during the *in utero* period.[34]

Susceptibility

1. Variation in several genes in the nitric oxide (NO) synthesis and inflammatory pathways, including NOS2A, ARG2, and 5-LO, are associated with eNO, susceptibility to air pollution, and asthma pathogenesis.[35-38]
2. Variants in cytokine genes are associated with exhaled NO and incident asthma [39-40]
3. The tumor necrosis factor (TNF)-308 GG genotype may have a protective role in asthma pathogenesis depending on airway oxidative stress levels.[41]
4. In children with at least one copy of the TNF-308 A variant, exposure to two or more household smokers is associated with a two-fold risk of a school absence due to respiratory illness (RI) and a four-fold risk of lower RI-related school absence compared with unexposed children with the TNF-308 GG genotype.[42]
5. Gluthathione-s-transferase M1 and PI (GSTM1 and GSTP1) modify the adjuvant effect of diesel exhaust particles on allergic inflammation.[17]
6. Certain variants in intercellular adhesion molecule-1 (ICAM-1) are associated with reduced risk for asthma. Differences in associations of asthma risk with ICAM-1 were found between African-Americans and non-Hispanic and Hispanic whites.[43-44]
7. High microsomal epoxide hydrolase (mEH) activity is associated with increased asthma risk and children with both high mEH activity and GSTP1 105Val are at the greatest risk.[45-46]
8. The clara cell secretory protein gene (CC16) variant allele at position 38 is associated with susceptibility to asthma and wheezing in African-Americans and the risk of early onset asthma among non-Hispanic Whites with a family history of asthma.[47]

9. Genes in glutathione regulation alter the effect of air pollution on lung function growth[48] and asthma.[49]
10. Dog ownership enhances symptomatic responses to air pollution in children with asthma.[50]
11. Decreased airway flows predict new onset asthma in preadolescent and adolescent children.[50-51]
12. Children with the val105 variant of GSTP1 may be protected from the increased risk of asthma associated with exercise, especially in high ozone communities.[52]
13. Functional promoter variants in HMOX-1 are associated with a reduced risk for new-onset asthma among non-Hispanic whites; this protective effect is largest in children residing in low-ozone communities.[53-54]
14. Genetic variation across the GST mu locus is associated with eight-year lung function growth.[55]
15. Children of mothers who smoked during pregnancy with variation in GSTM2 have lower lung function.[55]
16. Genetic variants in both the promoter and coding regions of the GSTP1 locus may contribute to the occurrence of childhood asthma and wheezing and may increase susceptibility to adverse effects of tobacco-smoke exposure.[56]
17. A positive association is seen between community-level socio-economic position and prevalent and incident childhood asthma, suggesting a significant role for environmental factors in the etiology of this disease.[57-58]
18. Parental stress increases the risk of childhood wheeze among children with no parental history of asthma, especially among boys.[59]
19. Parental stress and low socioeconomic status increase the risk of childhood wheeze and asthma associated with traffic-related air pollution.[60]

Mechanism

1. Exhaled NO is a useful biomarker for airway inflammation in large population-based studies. [61-63]
2. Exposure to particulate matter less than 2.5 microns in diameter ($PM_{2.5}$) mass concentration (two to seven-day average prior to the test) is associated with increased exhaled NO.[64]
3. Children with chronic airway inflammation, as indicated by elevated eNO, are at increased risk for new-onset asthma.[65]
4. Primary allergic sensitization may be prevented by initial high levels of respiratory allergen exposure through induction of a modified, nonallergic immune response.[66]
5. Evidence from controlled chamber experiments shows that secondhand smoke can exacerbate allergic responses in humans.[67]
6. A natural protective mechanism in B cells from oxidant pollutants, such as diesel particles, is the expression of phase II enzymes through induction of antioxidant response elements.[23]
7. Induction of phase II enzymes by the chemical sulforaphane can block DEP-induced enhanced IgE production in B cells and DEP-induced proinflammatory cytokine production in epithelial cells.[68]
8. Pretreatment with sulforaphane inhibits diesel-induced production of IL-8, granulocyte-macrophage colony-stimulating factor, and IL-1beta from primary human bronchial epithelial cells, demonstrating that sulforaphane can mitigate the effect of diesel in respiratory epithelial cells.[24]
9. A placebo-controlled dose escalation trial demonstrates that sulforaphane from broccoli sprouts induces a potent increase in antioxidant Phase II enzymes in airway cells and suggests enhancement of Phase II enzyme expression as a novel therapeutic strategy for oxidant induced airway disease.[69]

New Methodology

1. Offline eNO field measurements can predict online eNO with concurrent ambient NO measurements.[70-72]
2. Field-based extended NO testing of children yields useful information about NO at different levels of the respiratory tract, not obtainable from conventional eNO measurement [73]
3. The development of models to assess air pollution exposures within cities for assignment to subjects in health studies augments the field of exposure assessment and may help to reduce scientific uncertainties that now impede policy intervention aimed at protecting public health.[74]
4. Methods were developed to optimally locate a dense network of monitoring stations representing land use, transportation infrastructure, and the distribution of at-risk populations; this has widespread applicability for the design of pollution monitoring networks, particularly for measuring traffic pollutants with fine-scale spatial variability.[75]
5. Residential ozone concentrations may be over- or underestimated by measurements at a community monitor, depending on the variation in local traffic in the community.[76]
6. Statistical methods have been developed related to the general multi-level modeling paradigm, with a focus on flexible modeling techniques for nonlinear lung function trajectories in children and their relationship to air pollution. The models address many issues, including ecologic inference, multi-pollutant and subgroup analysis, simultaneous modeling of several outcomes, and exposure measurement error.[77]

7. A testing strategy called the "focused interaction testing framework" (FITF) was developed to identify susceptibility genes involved in epistatic interactions for case-control studies of candidate genes. In CHS data, FITF identified a significant multilocus effect between NQO1, MPO, and CAT, three genes involved in the oxidative stress pathway. In an independent data set, these three genes also show a significant association with asthma status.[78]
8. For analysis of a single candidate gene, the SNP interaction model with phase information (SIMPle) model can be used to identify important SNPs and underlying haplotype structures across a variety of causal models and genetic architectures.[79]
9. A two-step approach was developed to test association of disease with multiple single nucleotide polymorphisms (SNPs) within a candidate locus. The first step uses principal components (PCs) analysis to compute combinations of SNPs that capture the underlying correlation structure within the locus. The second step uses the PCs directly in a test of disease association.[80]
10. A two-step analysis of genome-wide association study data aimed at identifying genes involved in a gene-environment interaction was developed. The procedure complements standard screening for marginal genetic effects and has the potential to uncover novel genetic signals.[81]

Community Outreach and Translation

1. Traditional approaches to the calculation of attributable risk may underestimate the health impact of long-term environmental or other exposures that produce both chronic and acute disease.[82]
2. Community-based quantitative risk analyses can improve our understanding of health problems and help promote public health in transportation planning.[83-84]
3. As ports and goods movement activity expands throughout the United States, outreach efforts in the Center have made health and community impacts a more central part of policy discussions.[85-88]
4. The large population of children exposed to high levels of outdoor air pollutants and the substantial risks for adverse health effects presents unexploited opportunities to reduce the burden of asthma.[89]

BRIEF PROGRESS SUMMARIES PROJECTS

This Children's Environmental Health Center renewal supports a program of ongoing research examining the genetic and environmental determinants of respiratory diseases. Here we briefly highlight some of the most significant results from the previous five years of Projects 1 (McConnell) and 3 (Gilliland) that will continue.

Urban Air Pollution and Persistent Early Life

In the last five years, we have evaluated three hypotheses about traffic-related air pollution: 1) Prevalent asthma with early onset (in the first 5 years of life) is strongly associated with early life traffic within 100 m of the child's home; 2) Early onset asthma is independently associated with variation of NO, NO_2 and ozone within communities, which represent regional products of atmospheric photochemical oxidation of traffic related pollutants, but which also vary locally with traffic; 3) The effects of air pollutants on asthma risk in children are modified by polymorphisms in GSTM1, GSTP1, NQO1, HO-1, and TNFα, genes involved in response to oxidant air pollutants. We found that early life asthma that was symptomatic during the year prior to study entry at age 5-7 was associated with traffic proximity and with NO, NO2 and NOx estimated from dispersion models and traffic volume. There was a dose response relationship between distance to traffic corridors, with increased risk beginning approximately 200 m from a major road and increasing approximately linearly with proximity. The odds ratio was 1.6 for asthma within 75 m of major roads (including freeways, highways and major arterials) where 15% of all participants lived. Risk was larger in children with early life (and longer duration) exposure based on residence at the same address since age 2. Susceptible groups were identified, including increased risk in girls, consistent with previous literature. Risk of asthma symptoms, severity and prevalence (or asthma incidence in independently funded related work) associated with traffic-related local or regional air pollution was found to be modified by genetic variants involved in oxidative/nitrosative stress pathways, including GSTM1 and P1, TNFα, and EPHX1. The associations of lifetime asthma with NOx, NO2 and ozone measured in a case-control study were not significant. However, based on these and additional measurements at a total of over 1000 locations across southern California improved models predicting spatial surfaces of these pollutants in our study communities based on traffic distance, volume, meteorology, population density, and other nearby land use. Predicted exposure to NOx was associated with asthma and strongly associated with novel wheezy phenotype based on number and severity of symptoms. Regional pollution was not associated with asthma across study communities, after adjusting for local traffic-related exposure, although ozone was found to modify the effect of genetic variants on the risk of asthma and asthmatic bronchitis. This study was conducted as a community based participatory research (CBPR) project

in close coordination with COTC goals to develop community capacity to understand and apply research results to policy related prevention. In this context novel risk assessment methods were developed that identified a several-fold increase in air pollution-related emergency room visits and other severe asthma morbidity likely to result from increased asthma rates due to traffic proximity in the study communities of Long Beach and Riverside. Work with community partners to develop estimates of traffic volume on major traffic corridors has led to novel pilot work by Center investigator Scott Fruin to use these methods to improve our prediction model surfaces. CBPR is not explicitly a feature of the renewal application, as we have developed a new risk assessment initiative and a large pending grant application with the Air Quality Management District, our governmental partner in the last cycle of the CEHC. The renewal application is focused on developing a comprehensive estimate of the burden of disease surrounding major traffic corridors in LA County, including the 710 corridor that is the "laboratory" for COTC. Our community engagement "essential characteristic" for the proposal draws upon the strong community partnerships developed in our previous grant cycles, which has led to leveraging of funding by the COTC to establish a community/academic collaborative involving our two CBPR partner organizations and several new partners, described in more detail in the COTC section of this proposal.

Air Pollution, Exhaled Breath Markers and Asthma in Susceptible Children (now Project 2: PM, Extended eNO, Susceptibility, and Lung Development)

In the past five years, we assessed three hypotheses based on a biological model for the oxidative stress and inflammatory pathways involved in the pathogenesis of adverse effects of air pollution: (1) High ambient air pollution exposure is associated with chronic airway inflammation in children as indicated by elevated exhaled NO (eNO), a marker of airway inflammation and oxidative/nitrosative stress; (2) Children's susceptibility to airway inflammation and oxidative/nitrosative stress from ambient air pollution varies by NOS1, NOS2 and NOS3, GSTM1, GSTP1, NQO1, and HO-1 genotypes; and (3) Children with chronic airway inflammation as indicated by elevated eNO are at increased risk for new onset asthma. We first investigated whether high ambient air pollutant exposures were associated with elevated eNO (marker of inflammation) in more than 2700 children. We found that exposures to particulate matter less than 2.5 microns in diameter ($PM_{2.5}$) mass concentration (two to seven-day average prior to the test) were associated with increased eNO. In order to investigate the second hypothesis, we assessed whether specific genetic variants were associated with airway inflammation (elevated eNO) and children's susceptibility to airway inflammation from ambient air pollution. We found strong evidence that variation in several genes on the nitric oxide (NO) synthesis pathway, including NOS2A and ARG2, are associated with eNO, susceptibility to air pollution, risk of new onset asthma and lung function growth. Finally, in order to evaluate hypothesis 3, we investigated whether elevated exhaled NO at baseline is associated with new onset asthma during the follow-up period. We determined that children with chronic airway inflammation as indicated by elevated eNO are at increased risk for new onset asthma. Taken together, these findings support the hypothesis that ambient PM produces inflammation and oxidative/nitrosative stress in the airways and provide evidence that airway inflammation/nitrosative stress contributes to asthma pathogenesis and abnormal lung function development. Furthermore, these findings indicate that variants in genes involved in NO production pathways may affect susceptibility to the adverse effects of air pollution. Based on preliminary data, studies of genes and pathways involved in regulating inflammatory responses are likely to provide crucial information needed to understand the role of the interrelated processes of oxidative/nitrosative stress on inflammation in respiratory disease pathogenesis. The renewal application proposes to build on the unique resources of the CEHC by taking the next steps in filling important gaps in the knowledge base.

: Pollution-Enhanced Allergic Inflammation and Phase II Enzymes

Aim #1: We will test the hypothesis that Phase II enzyme expression in the upper airways are induced by oxidant pollutants and differ between children and adults. We had previously shown that challenge of individuals with diesel exhaust particles (DEP) induced GSTM1 expression in adults.

We expanded these studies and completed similar challenges in 20 children. In adults, DEP induced expression of GSTP1 in a dose-dependent fashion. With increasing concentrations of DEP challenge, there

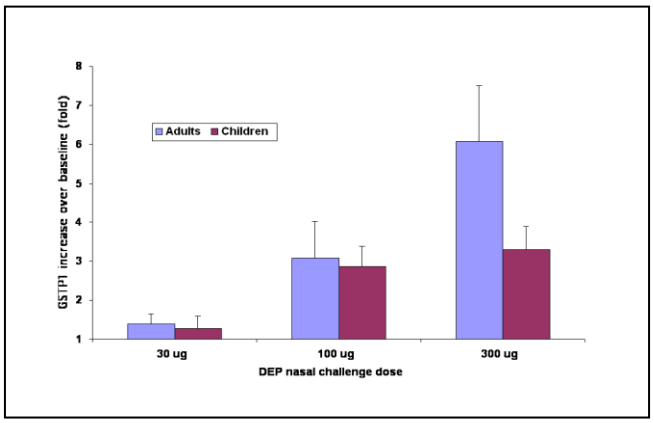

Figure 2 GSTP1 response to DEP in adults vs. children

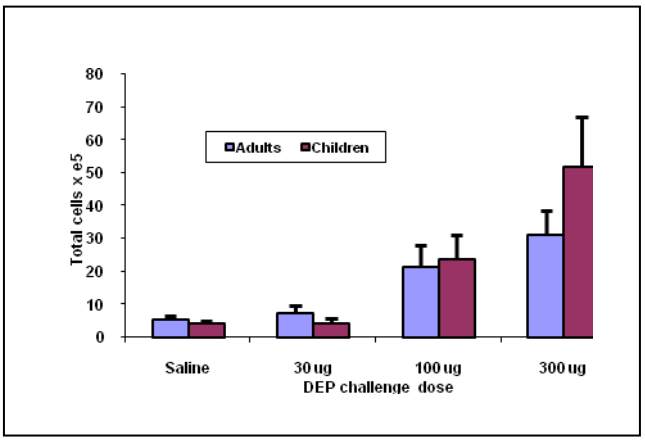

Figure 3 Cellular response to DEP in adults vs. children

were higher levels of GSTP1-relative gene expression. Cellular infiltration was inversely correlated with GSTP1 enzyme gene expression. Increased levels of GSTP1 were associated with lower cell count numbers. In children, the degree of cellular infiltration also correlated with dose of nasally administered DEP challenge. Higher concentrations of DEP elicited a larger number of total cells recovered from nasal lavage fluid obtained 24 hours after DEP exposure. However, as compared to adults, this effect in children was more robust at the DEP challenge of 300 µg. In these children, DEP also induced expression of GSTP1. At DEP concentrations of 30 and 100 µg, there were higher levels of GSTP1-relative gene expression. However, *GSTP1-relative gene expression for the DEP nasal challenge of 300 µg was decreased in children as compared to adults.* Similar results were seen with the other three measured Phase II enzymes.

Aim#3: We will determine the role of Phase II enzymes in regulating the adjuvant effects of PM.
We have previously shown that enhancement of Phase II enzyme expression could inhibit enhancement of IgE production by peripheral blood cells *in vitro***.** In those experiments, we used sulforaphane—a potent inducer of Phase II enzymes found in cruciferous vegetables. We tested whether this same reagent could block DEP-mediated adjuvant events *in vivo* in a murine model. Groups of six female BALB/c mice matched for age and weight (10-12 weeks) received aerosolized exposures to either saline, ovalbumin (OVA) (1% 20 min), DEP (1 hr) or OVA followed immediately by DEP for ten consecutive days. Mice were administered either vehicle (corn oil) or sulforaphane (4.5 µmol/mouse/day) by gavage (0.2 ml) for one week prior to the commencement of exposures up until two days after the last exposure. As expected, in the untreated group, IgG1 levels were significantly higher in mice who received both DEP and OVA than in those who were exposed to OVA alone. However, administration of sulforaphane completely ablated the adjuvant effects of DEP.

We then examined the responses of the airway epithelial cell line BEAS-2B and primary normal human bronchial epithelial cells upon treatment with sulforaphane and Phase II enzymes followed by stimulation with diesel extract (0-25 µg/ml). As expected, sulforaphane upregulated the expression of endogenous antioxidant enzymes in bronchial epithelial cells. Whereas diesel extract stimulated the production of IL-8, GM-CSF, and IL-1β from normal human bronchial epithelial cells, pre-treatment with sulforaphane for 24 hours inhibited diesel-induced cytokine production in a dose-dependent fashion. These studies suggest that sulforaphane treatment can prevent the production of pro-inflammatory cytokines in respiratory epithelial cells *in vitro*.

Previously, we reported that individuals who lack the ability to make the Phase II enzyme GSTM1 are at increased risk for the pro-inflammatory effects of DEP, and we have shown that enhancement of Phase II enzymes with sulforaphane can inhibit the production of pro-inflammatory cytokines in respiratory epithelial cells *in vitro*. In order to determine whether GSTM1 itself is important in the regulation of inflammatory response to pollutants, we used siRNA to “knock down” the GSTM1 gene in bronchial epithelial cells. Expression could be reduced by more than 90% using this methodology. Knockdown of GSTM1 augmented DEP induced cytokine production in these cells. Thus, IL-8 levels were almost three-fold higher in cells where GSTM1 expression was reduced, compared to sham-treated cells.

Finally, in a placebo-controlled dose escalation trial to investigate the *in vivo* effects of sulforaphane, we demonstrated that consumption of oral sulforaphane contained in broccoli sprouts homogenate (BSH) can

induce a potent increase in antioxidant Phase II enzymes in airway cells. RNA expression for GSTM1, GSTP1, HO-1 and NQO1 was measured in nasal lavage cells by RT-PCR before and after sulforaphane dosing. Increased Phase II enzyme expression occurred in a dose-dependent manner with maximal enzyme induction observed at the highest dose of 200 g broccoli sprouts prepared as BSH. Significant increases were seen in all sentinel Phase II enzymes RNA expression compared to baseline. Phase II enzyme induction was not seen with ingestion of non-sulforaphane containing alfalfa sprouts. These findings suggest enhancement of Phase II enzyme expression as a novel therapeutic strategy for oxidant-induced airway disease.[69]

Our results show that Phase II enzymes can be induced by our model air pollutant, DEP, and are critical in regulating responses and determining susceptibility to these xenobiotics. A principal finding of our results is the discovery that children have enhanced inflammatory responses to the model pollutant DEP and that this seems to be related to their reduced capacity to make a cytoprotective Phase II enzymes response. Our studies illuminate why there may be increased susceptibility of certain vulnerable individuals and populations (such as children) to oxidant pollutants and suggest that increasing the body's Phase II responses either by therapeutic or dietary means may counteract this effect. Moreover, the discovery that *in vitro* GST expression is associated with *in vivo* inflammatory responses provides the potential to develop a diagnostic test for susceptibility to oxidant pollutants.

RP.2.4 PUBLICATIONS RESULTING FROM THE CHILDREN'S CENTER (2004–2009)

Publications resulting from collaborations between projects are starred with an asterisk.

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RP.2.5 SUMMARY OF THE KEY SCIENTIFIC CONTRIBUTIONS OF THE CENTER

The key scientific findings have been presented in Section RP.2 Program Accomplishments. These findings clearly demonstrate that ambient air pollution at current levels has clinically important adverse acute and chronic health effects on children that are likely to contribute to a lifetime of sub-optimal health. The role of PM in causing acute effects has emerged as an important topic of research and progress has been made in understanding these effects.[90-91] Mechanisms appear to involve oxidative/nitrosative stress and inflammatory pathways. New reports suggest that the chronic effects of PM may be greater than the acute effects[8, 92] and that consideration of microenvironments and physical activity patterns might be critical. Although the chronic effects of PM are likely to be important, few studies have approached the difficult task of investigating the chronic effects of long-term exposures across the life course. The extensive CHS resources, the levels of

exposure in southern California, the new analytic methods and the experience and highly collaborative multidisciplinary team contribute to the high probability that the program of research proposed in this application will fill key gaps in the knowledge base to advance our scientific understanding of respiratory disease in general, and the specific contribution of air pollution to the occurrence of respiratory diseases.

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